OBJECTIVES

1. To review the efficacy, safety, and administration of the currently available fluoroquinolones.

Generic Name	Trade Name(®)	Manufacturer
Ciprofloxacin	Cipro	Bayer
Enoxacin	Penetrex	Rhone-Poulenc Rorer
Gatifloxacin	Tequin	Bristol Myers Squibb
Levofloxacin	Levaquin	Ortho-McNeil
Lomefloxacin	Maxaquin	Searle
Moxifloxacin	Avelox	Bayer
Norfloxacin	Noroxin	Merck
Ofloxacin	Floxin	Ortho-McNeil

Sparfloxacin and trovafloxacin will not be reviewed because of their limited clinical use and their adverse event profiles.

2. To define selection criteria when contracting these agents for the Veterans Health Administration.

I. PHARMACOLOGY AND RESISTANCE[1-12]

The fluoroquinolones are synthetic, broad-spectrum antibacterial agents with bactericidal activity. They exert their effects by binding to and inhibiting bacterial DNA-gyrase. This enzyme produces supercoiling of cellular DNA which is needed for bacterial DNA synthesis.

The addition of a fluorine atom to nalidixic acid at position 6 increased the antimicrobial potency with both gram-positive and gram-negative organisms. The piperazine substituent is responsible for the antipseudomonal activity of the fluoroquinolones. The inclusion of an 8-methoxy group resulted in the ability to decrease the selection of quinolone resistant mutations. Levofloxacin is the L-isomer of ofloxacin, which is responsible for antibacterial effects.

Fluoroquinolone resistance is caused by alterations in DNA gyrase, decreased penetration through the outer cell membrane, and by increased export of the fluoroquinolones by efflux pumps. Cross-resistance has been reported with these agents, and may effect other classes of antimicrobial drugs. Resistance to the earlier fluoroquinolones has become prevalent in infections caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Serratia marcescens*. The resistant strains of methicillin-resistant *S. aureus* have been reported as high as 79% after the introduction of fluoroquinolones to hospital drug formularies. The prophylactic

use of the fluoroquinolones in neutropenic patients has been reported to correlate with coagulase negative staphylococcus resistance.

II. MICROBIOLOGY[1-8]

Table 1 summarizes the activity of the fluoroquinolones against microorganisms both in vitro and in clinical infections. The table is limited to microorganisms associated with FDA approved indications. In clinical practice, there may be usage outside of these indications. As with any antibacterial agent, appropriate culture and sensitivities should be performed prior to initiating therapy with the fluoroquinolones. Appropriate therapy should be given once these results become available.

The fluoroquinolones are broad-spectrum antibacterial agents with in vitro activity against many gram-negative and gram-positive organisms. The newer fluoroquinolone agents have greater gram-positive activity as compared to agents such as ciprofloxacin and ofloxacin (see Table2). Breakpoint data recommended by National Committee for Clinical Laboratory Standards (NCCLS) has been included in Table 3, to facilitate appropriate interpretation of MIC values in Table 2.

Table 1. Antimicrobial Spectrum of the Fluoroquinolones

ORGANISM	Ciprofloxacin	Enoxacin	Gatifloxacin	Levofloxacin	Lomefloxacin	Moxifloxacin	Norfloxacin	Ofloxacin
Gram-negative								
Campylobacter sp	X							
Citrobacter sp	X	*	*	*	X	*	X	X
Enterobacter sp	X	X	*	X	X	*	X	X
Escherichia coli	X	X	X	X	X	*	X	X
Haemophilus influenzae	X		X	X	X	X		X
Haemophilus parainfluenzae	X		X	X		X		
Klebsiella pneumoniae	X	X	X	X	X	X	X	X
Legionella sp	*		X	X	*	*		*
Moraxella catarrhalis	X		X	X	X	X		
Morganella morgani	X	*	*	*	*	*	*	*
Neisseria gonorrhoeae	X	X	X				X	X
Proteus mirabilis	X	X	X	X	X	*	X	X
Proteus vulgaris	X	*	*	*	*		X	*
Pseudomonas aeruginosa	X	X		X	X		X	X
Salmonella sp	X		X	*		X		*
Serratia sp	X			*			X	
Shigella sp	X		X	*		X		
Gram-positive								
Staphylococcus Aureus	X		X	X		X	X	X
S. epidermidis	X	X	X			X		
S. saprophiticus	X	X			X			
Enterococcus sp	X		X	X		X	X	
Streptococcus pneumoniae	X			X				X
S. pyogenes	X			X				X
Other								
Chlamydia pneumoniae			X	X		X		
Chlamydia trachomatis								X
Mycoplasma pneumoniae			X	X		X		
Anaerobe								
Bacteroides fragilis								
Peptostreptococcus sp.			*			*		
Clostridium perfinges				*			*	*

X microorganisms associated with FDA approved indications.

* Exhibits in vitro MIC of $\leq$1 mcg/ml(ciprofloxacin), $\leq$ 2 mcg/ml (enoxacin, gatifloxacin,levofloxacin,lomefloxacin,moxifloxacin,ofloxacin), $\leq$4 mcg/ml(norfloxacin) against $\geq$90% strains however, the safety and effectiveness in treating clinical indications has not been established in adequate well controlled clinical trials.

Table 2. Comparison of Minimum Inhibitory Concentrations (MIC) (values shown are 90% MIC (mcg/ml)

ORGANISM	Ciprofloxacin	Enoxacin	Gatifloxacin	Levofloxacin	Lomefloxacin	Moxifloxacin	Norfloxacin	Ofloxacin
Gram-negative								
Campylobacter sp								
Citrobacter sp								
Enterobacter sp								
Escherichia coli	0.004 - 0.015	0.06-0.25	0.016-0.25	0.008 – 0.06	0.03-0.12	0.008-1.0	0.03 – 0.12	0.015 – 0.12
Haemophilus influenzae	0.008		0.008-0.06	0.008 – 0.03	0.12	0.03-0.12		0.016 – 0.06
Haemophilus parainfluenzae								
Klebsiella pneumoniae	0.06		0.06-2.0	0.25	0.5	0.06-0.25		0.12
Legionella sp	0.5		0.016-0.38	0.06		0.016		0.12
Moraxella catarrhalis	0.03		<0.001-0.03	0.03	0.25	<0.001-0.06		0.12
Morganella morgani						0.13-1.0		
Neisseria gonorrhoeae		0.015 – 0.06	0.004-0.008			0.015		0.004 – 0.016
Proteus mirabilis	0.03		0.12-1.0		0.5	0.025-0.25		0.12
Proteus vulgaris			0.25-1.0			0.025-0.5		
Pseudomonas aeruginosa	0.25 – 1.0	2.0 – 8	4.0-32.0	0.5 – 4.0	1.0 – 4.0	4.0-32.0	1.0 – 4.0	1.0 – 8.0
Salmonella sp			0.06-0.25			0.03-0.12.		
Serratia sp			0.06-4.0			0.06-4.0		
Shigella sp			<0.01-0.03			<0.01-0.03		
Gram-positive								
Staphylococcus Aureus	0.12 – 0.5	0.5 – 2.0	0.06-2.0	0.06 – 0.5	0.25 – 2.0	0.06-1.0	0.05 – 2.0	0.12 – 1.0
S. epidermidis			0.25-3.13			0.13-2.0		
Enterococcus sp	0.25 – 2.0	2.0 – 16	0.5-8.0	0.25 – 2.0		0.5-8.0	2.0 – 8.0	
Streptococcus pneumoniae	4.0		0.06-4.0	0.5 – 2.0	8.0	0.06-4.0		2.0
S. pyogenes	2.0		0.25-0.5	0.5	8.0	0.25-0.5		4.0
Other								
Chlamydia pneumoniae	1.0		0.06-0.25	0.5		0.03-0.5		1.0
Mycoplasma pneumoniae	2.0		0.06-0.13	0.5		0.06-0.12		2.0

Table 3. NCCLS Breakpoints(mcg/ml) for Interpretive Categories[a]

Agent	Susceptible	Intermediate	Resistant
Ciprofloxacin	1	2	4
Gatifloxacin	2	4	8
Levofloxacin	2	4	8
Moxifloxacin	2	4	8
Ofloxacin	2	4	8

[a] Adapted from National Committee for Clinical Laboratory Standards: Performance Standards for Antimicrobial Disk Susceptibility Test, 1990

III. FDA APPROVED INDICATIONS[1-9]

The fluoroquinolones are indicated for the treatment of the following infections caused by susceptible strains of designated microorganisms.

Table 4. FDA Approved Indications for the Fluoroquinolones

	ciprofloxacin	enoxacin	gatifloxacin	levofloxacin	lomefloxacin	moxifloxacin	norfloxacin	ofloxacin
Site								
Urinary Tract	X	X	X	X	X		X	X
Lower Respiratory Tract	X[a]		X	X	X[a]	X		X[a]
Bone and Joint	X							
Infectious Diarrhea	X							
Skin & Skin Structure	X		unlabeled	X				X
Sexually Transmitted Diseases	X	X	X				X	X
Prostatitis	X		Unlabeled	unlabeled			X	X
Pelvic Inflammatory Disease								X
Acute Sinusitis	X		X	X				
Intra-Abdominal Infections	X					X		
Typhoid Fever	X							
Pyelonephritis				X				

[a] Not the first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*.

IV. PHARMACOKINETICS[1-9,13,14] (Table 4)

In general, the fluoroquinolones are well absorbed and distribute readily through most tissues. Enoxacin and norfloxacin do not achieve adequate serum concentrations and thus are limited to infections of the genitourinary or urinary tract. The serum elimination half-life of the fluoroquinolones range from 3 – 20 hours, allowing for once or twice daily dosing. Because the major elimination route is via the kidney, dosage adjustment is required for these agents in patients with renal impairment.

Table 5. Fluoroquinolone Pharmacokinetic Profiles[a]

PARAMETER	Ciprofloxacin (I.V./oral)	Enoxacin	Gatifloxacin (I.V./oral)	Levofloxacin (I.V./oral)	Lomefloxacin	Moxifloxacin	Norfloxacin	Ofloxacin (I.V./oral)
Bioavailability (%)	70-80	90	96	99	95-98	90	30-40	98
Maximum Serum Concentration mcg/ml (dose)	1.2(250mg) 2.4(500 mg) 4.3(750mg) 5.4(1000mg)	0.8(200mg) 2(400mg)	2.4(200 mg) 4.2(400 mg)	2.8(250mg) 5.1(500mg)	1.4(200mg) 3.2(400mg)	4.5 (400 mg)	0.8(200mg) 1.5(400mg)	1.5(200g) 2.4(300mg) 2.9(400mg)
Area under curve (AUC) Mcgxhr/ml (dose)	4.8(250 mg) 11.6(500mg) 20.2(750mg) 30(1000mg)	16(400mg)	16.8(200 mg) 35 (400 mg)	27.2(250mg) 47.9(500mg)	10.9(200mg) 26.1(400mg)	48 (400 mg)	5.4(400mg)	14.1(200mg) 21.2(300mg) 31.4(400mg)
Protein Binding(%)	20-40	40	20	24-38	10	50	10-15	32
Major Elimination Route	Renal/hepatic	Renal /hepatic	renal	Renal	Renal	Renal/hepatic	Renal /hepatic	Renal
Half-Life (hours)	4/5-6	3-6	7-12	6-8/6-8	8	12	3-4.5	5-7/5-10
Effect of food on absorption	Delayed	Not Available	None	Delayed Reduced 14%	Delayed Reduced 12%	None	Delayed	Delayed

[a]Adapted from Hebel SK, ed. Drug Facts and Comparisons 2001.

V. SAFETY AND ADMINISTRATION[1-10,15-21]

The most common adverse events experienced with fluoroquinolone administration are gastrointestinal (nausea, vomiting and diarrhea), which have been reported in 1 to 5% of patients. Central nervous system side effects such as headache and dizziness have been reported in few patients. Insomnia was reported in 3-7% of ofloxacin recipients. Phototoxicity has been reported for all drugs of this class with rates from 0.5-3%. The rank order of phototoxic potential is as follows: enoxacin> ciprofloxacin > norfloxacin = ofloxacin = levofloxacin = gatifloxacin = moxifloxacin.[18,19] Exposure to direct and indirect sunlight or UV lamps may precipitate the reaction. It may take as long as 3 weeks post discontinuation for a skin reaction to develop. The use of sunscreens with UVA and UVB should be recommended.

One of the most concerning adverse events has been associated with QT prolongation and the fluoroquinolones. Indeed, several agents have been withdrawn from the market due to this rare but life threatening adverse effect. Clinical trials with moxifloxacin have reported a mean 6 msec QT prolongation in 38 patients out of 4,008. There was one cardiovascular event in these patients.[20] The majority of the FDA advisory panel which reviewed the agent for approval did not feel the reported events were of concern but warranted post marketing study and follow-up. Since moxifloxacin is not metabolized in the P450 system there would not be the additive concern of increasing drug accumulation and risk of QT prolongation as seen with other agents (terbinafine, cisapride). No cardiovascular events associated with QT prolongation in over 4000 patients receiving gatifloxacin have been reported.[21]

Due to limitations in the FDA drug approval process, the true adverse effect profile for a medication may not be known until it is prescribed for large numbers of patients. Serious adverse effects that occur only rarely may not be evident for several years. Table 6 lists the numbers of patients exposed to some of the newer fluoroquinolones. Data was obtained from the pharmaceutical manufacturer.

Table 6: Patient Exposures to Fluoroquinolones (as of Nov 2000)

Drug	US	Worldwide
Gatifloxacin	1,124,000 outpatient exposures (New prescriptions written)	150,000 outpatient exposures in addition to US prescriptions
Ciprofloxacin	125,000,000 patient lives	125,000,000 additional patients lives
Moxifloxacin	1,250,000 patient lives	1,250,000 additional patient lives
Levofloxacin	100,000,000 patient lives	50,000,000 additional patient lives

Rupture of the shoulder, hand and Achilles tendons has been reported in patients using quinolones. Cartilage damage has been reported with the use of fluoroquinolones in immature animals. The safety and efficacy of the fluoroquinolones have not been established in patients under the age of 18 years old, pregnant women, or lactating women.

Patients should be instructed to drink fluid liberally during treatment with any of the fluoroquinolones in order to prevent crystal formation in the urine. Norfloxacin and enoxacin should be administered 1 hour before or 2 hours after a meal to ensure adequate absorption. Preferably, ciprofloxacin should be administered 2 hours after a meal.

VI. DRUG INTERACTIONS[1-9,15,16,22]

Various drug-drug interactions can occur with the use of the quinolones. Absorption of the quinolones is significantly diminished with the concomitant use of compounds that contain multivalent metal cations such as aluminum, magnesium, zinc, iron, and calcium. Other interactions with the quinolones involve metabolism and clearance. Table 7 lists drug interactions that may occur with the quinolones.

Table 7. Drug Interactions with the Fluoroquinolones[a]

Fluoroquinolone	Drug(s)	Interaction	Clinical relevance
All	Antacids,didanosine,iron salts,sucralfate,zinc salts	Reduced GI absorption of fluoroquinolone.	Give 2 hours after or 6 hours before quinolone.
Ciprofloxacin	Diazepam	Increased plasma concentrations of diazepam.	Clinical significance unknown. Monitor for prolonged effects of diazepam.
Ciprofloxacin	Foscarnet	Unknown	Tonic clonic seizures occurred in 2 patients receiving both drugs. Further study is warranted.
Enoxacin	Bismuth subsalicylate	Reduced enoxacin bioavailability.	Space apart by at least 1 hour.
Ciprofloxacin	Metoprolol	Reduced oral metoprolol (+) and (-); clearance by 54% and 29%, respectively.	Clinical significance unknown.
Norfloxacin	Nitrofurantoin	Antibacterial effect of norfloxacin in the urinary tract may be antagonized.	Combination not recommended.
Ciprofloxacin	Pentoxifylline	Reduced metabolism of pentoxifylline.	Increased risk of side effects of pentoxifylline (eg. headache).
Ciprofloxacin,enoxacin,norfloxacin	Caffeine	Total body clearance of caffeine is reduced by up to 75%.	Minimize caffeine intake.
Enoxacin	Digoxin	Digoxin levels may be increased.	Monitor for signs and symptoms of digoxin toxicity.
Ciprofloxacin	Hydantoins	Phenytoin levels may be increased or decreased.	Conflicting data exist. Monitor for signs of phenytoin toxicity.
Ciprofloxacin,enoxacin,norfloxacin, Lomefloxacin,ofloxacin	Anticoagulants	The effect of the anticoagulant may be increased.	Conflicting data exist. Monitor prothrombin time.
Ciprofloxacin,enoxacin,norfloxacin, Ofloxacin	Theophylline	Decreased clearance and increased theophylline plasma levels.	Avoid combination. Theophylline toxicity can occur.
All	Non-steroidal anti-inflammatory agents (fenbufen)	Combination may enhance inhibition of γ-aminobutyric acid leading to CNS stimulation.	More likely to occur in patients with epilepsy of a history of convulsions.

[a]Adapted from Hebel SK, ed. Drug Facts and Comparisons 2001, and Hansten PD, ed. Drug Interactions Analysis and Management 1999.

VII. DOSING[1-9]

The fluoroquinolones are dosed based on the site and severity of the infection. The following tables provide dosing recommendations based on FDA indications.

Table 8. Urinary Tract Infections

Drug	Oral Dose	Intravenous Dose	Interval	Duration
Ciprofloxacin	250-500mg	200-400mg	Q 12 H	7-14 days
Enoxacin	200-400mg		Q 12 H	7-14 days
Gatifloxacin	200-400mg	200-400	QD	Uncomplicated single dose or three days. Complicated 7-10 days
Levofloxacin	250mg	250mg	Q 24 H	10 days
Lomefloxacin	400mg		Q 24 H	10-14 days
Norfloxacin	400mg		Q 12 H	7-14 days
Ofloxacin	200mg	200mg	Q 12 H	7-10 days

Table 9. Lower Respiratory Tract Infections

Drug	Indication	Oral Dose	Intravenous Dose	Interval	Duration
Ciprofloxacin	Mild/moderate Severe/complicated Nosocomial Pneumonia	500mg 750mg	400mg 400 mg[c] 400mg	Q 12 H Q 12 H Q 8 H	7-14 days 7-14 days
Gatifloxacin	ABECB/CAP	400mg	400mg	Q 24 H	7-10 days
Levofloxacin	ABECB[a] CAP[b]	500mg 500mg	500mg 500mg	Q 24 H Q 24 H	7 days 7-14 days
Lomefloxacin	ABECB[a]	400mg		Q 24 H	10 days
Moxifloxacin	ABECB/CAP	400mg		Q 24 H	5-10 days
Ofloxacin	ABECB[a] CAP[b]	400mg 400mg	400mg 400mg	Q 12 H Q 12 H	10 days 10 days

[a]Acute bacterial exacerbation of chronic bronchitis
[b]Community acquired pneumonia
[c]Interval for intravenous dose is Q 8 H in severe infection

Table 10. Bone and Joint Infections

Drug	Indication	Oral Dose	Intravenous Dose	Interval	Duration
Ciprofloxacin	Mild/moderate Severe/complicated	500mg 750mg	400mg 400mg[a]	Q 12 H Q 12 H	7-14 days 7-14 days

[a]Interval for intravenous dose is Q 8 H in severe infection

Table 11. Infectious Diarrhea

Drug	Indication	Oral Dose	Intravenous Dose	Interval	Duration
Ciprofloxacin	Mild/moderate/severe	500mg	400mg	Q 12 H	5-7 days

Table 12. Skin and Skin Structure Infections

Drug	Indication	Oral Dose	Intravenous Dose	Interval	Duration
Ciprofloxacin	Mild/moderate Severe/complicated	500mg 750mg	400mg 400 mg[a]	Q 12 H Q 12 H	7-14 days 7-14 days
Levofloxacin	Uncomplicated	500mg	500mg	Q 24 H	7-10 days
Ofloxacin	Uncomplicated	400mg	400mg	Q 12 H	10 days

[a] Interval for intravenous dose is Q 8 H in severe infection

Table 13. Sexually Transmitted Diseases

Drug	Indication	Oral Dose	Intravenous Dose	Interval	Duration
Ciprofloxacin	Uncomplicated Gonorrhea	250mg		Single Dose	Single Dose
Enoxacin	Uncomplicated Gonorrhea	400mg		Single Dose	Single Dose
Gatifloxacin	Uncomplicated urethal gonorrhea, endocervical and rectal gonorrhea in women	400mg		Single dose	
Norfloxacin	Uncomplicated gonorrhea	800mg		Single Dose	Single Dose
Ofloxacin	Uncomplicated Gonorrhea	400mg	400mg	Single Dose	Single Dose
	C trachomatis Urethritis/cervicitis	300mg	300mg	Q 12 H	7 days
	C trachomatis/ N gonorrhoeae Urethritis/cervicitis	300mg	300mg	Q 12 H	7 days

Table 14. Prostatitis

Drug	Indication	Oral Dose	Intravenous Dose	Interval	Duration
Ciprofloxacin	Chronic	500mg		Q 12 H	28 days
Norfloxacin	Acute and Chronic	400mg		Q 12 H	28 days
Ofloxacin		300mg	300mg	Q 12 H	6 weeks[a]

[a]Safety data is unavailable for intravenous use past 10 days

Table 15. Sinusitis

Drug	Indication	Oral Dose	Intravenous Dose	Interval	Duration
Ciprofloxacin	Acute	500mg		Q 12 H	10 days
Gatifloxacin	Acute	400mg		Q 24 H	10 days
Levofloxacin	Acute	500mg	500mg	Q 24 H	10-14 days
Moxifloxacin	Acute	400mg		Q 24 H	10 days

Table 16. Intra-Abdominal Infections

Drug	Indication	Oral Dose	Intravenous Dose	Interval	Duration
Ciprofloxacin(in Combination with metronidazole)	Complicated	500mg	400mg	Q 12 H	7-14 days

Table 17. Typhoid Fever

Drug	Indication	Oral Dose	Intravenous Dose	Interval	Duration
Ciprofloxacin	Mild/moderate	500mg		Q 12 H	10 days

Table 18. Pyelonephritis

Drug	Indication	Oral Dose	Intravenous Dose	Interval	Duration
Gatifloxacin	Acute	400mg	400mg	Q 24 H	7-10 days
Levofloxacin	Mild/moderate	250mg	250mg	Q 24 H	10 days

Table 19. Pelvic Inflammatory Disease

Drug	Indication	Oral Dose	Intravenous Dose	Interval	Duration
Ofloxacin	Acute	400mg	400mg	Q 12 H	10-14 days

VIII. RENAL DOSAGE ADJUSTMENTS[1-9,13]

Table 20. Fluoroquinolone Dosage Adjustments in Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose	Frequency
Ciprofloxacin	30-50 5-29 dialysis	250-500mg 250-500mg 250-500mg	Q 12 H Q 18 H Q 24 H (post-dialysis)
Enoxacin	30 or less	½ recommended dose	Q 12 H
Gatifloxacin	<40 ml/min dialysis	400mg X 1; then 200mg 400mg X 1; then 200mg	Q 24 H Q 24 H
Levofloxacin	20-49 10-19 dialysis	500mg x1; then 250mg 500mg x1;then 250mg 500mgx1; then 250mg	Q 24 H Q 48 H Q 48 H
Lomefloxacin	11-39 dialysis	400mgx1;then 200mg 400mgx1;then200mg	Q 24 H Q 24 H
Norfloxacin	<30	400mg	Q 24 H
Ofloxacin	20-50 <20	200-400mg 100-200mg	Q 24 H Q48 H

IX. COMPARATIVE TRIALS[23-34]

Few head to head comparative trials exist with the fluoroquinolones. The following tables summarize clinical trials that are published or in abstract form. In general, there were no statistically significant differences among the study groups in the various diagnoses.

Table 21. Urinary Tract Infections

Quinolone (n)	Design	Important Criteria	Results
Levofloxacin (L)250mg qd (126) Ciprofloxacin(C) 500mg bid (113) Richard et al (reference #23)	Randomized Double-blind Multicenter	Complicated UTI Urine culture with ≥ 10^5 cfu/ml Clinical signs/symptoms	Predominant organism *E. coli* Clinical success similar 88%(C) vs. 92%(L) Bacterial eradication 97%(C) vs. 94%(L) Adverse events similar L(4%) vs C(3%) with C GI symptoms with both Dizziness with L
Lomefloxacin(L) 400mg qd (72) Ciprofloxacin (C) 500 mg q12h (70) Cox et al (reference #25)	Randomized Single-blind	Complicated or Recurrent UTI Urine culture with ≥ 10^5 cfu/ml Clinical signs/symptoms	Predominant organism *E. coli* Bacterial efficacy 97.2%(L) vs. 95.7%(C) Clinical success 98.6%(L) vs. 95.7%(C) 5 patients in each group experienced adverse events (Gastrointestinal complaints or pruritis)
Levofloxacin (L) 250mg qd (171) Lomefloxacin (LM) 400mg qd (165) Klimberg et al (reference #26)	Randomized Non-blind, multicenter	Complicated UTI or Acute pyelonephritis	Predominat organism *E. coli* Bacteriological eradication 95.3% (L) vs. 92.1% (LM) Clinical success rate 92.9% (L) vs. 88.5% (LM)More adverse events with LM vs L(7.9% vs 4.3%)
Lomefloxacin(L) 400mg qd (220) Norfloxacin(N) 400mg bid (216) Iravani et al (reference #27)	Randomized,multicenter, Single-blind Mostly female	Uncomplicated UTI 2 urine cultures with≥10^5 cfu/ml Clinical signs/symptoms Excluded if resistant organisms at baseline	Predominant organism *E. coli* Bacteriologic efficacy Similar 98.2%(L) vs. 96.4% (N) Clinical success higher with L vs. N; 99% vs. 93.5% (p=0.002) More adverse events with L vs. N (11% vs. 7.6%) GI effects similar, dizziness more with L

Table 21 Urinary Tract Infections (continued)

Lomefloxacin(L) 400mg qd (55) Norfloxacin(N) 400mg bid (49) Nicolle et al (reference #28)	Short Course (3 days) Randomized, multicenter Single-Blind Female	Uncomplicated UTI Clinical signs/symptoms Excluded if fever present	Predominant organism *E. coli* The primary reason for withdrawl was treatment failure and was similar in both groups (7-8%) Bacterial eradication rates similar 98%(L) vs. 96%(N) Cure rates similar 93%(L) vs.98%(N) About 25% of pts reported adverse events (related) in each group Nausea, headache were most commonly reported
Norfloxacin(N) 400mg bid (29) Ciprofloxacin(C) 500mg q12h (29) Schaeffer et al (reference #29)	Randomized,two-center	Complicated UTI Urine culture with $\geq 10^5$ cfu/ml	Predominant organism *E. coli* Clinical cure (including bacterial eradication) similar 72%(N) vs. 79 %(C) Adverse events similar 3 patients experienced related adverse events with N; 1 patient with C
Lomefloxacin(L) 400mg qd (149) Ciprofloxacin(C) 500mg bid (129) Pisani et al (reference #30)	Randomized Multicenter	Complicated UTI Urine culture with >/= 10^5 cfu/ml Excluded if resistant organisms at baseline	Predominant organism *E. coli* Bacterial efficacy similar 87%(L) vs. 81%(C) Clinical success rates 85%(L) vs. 76%(C) No statistically significant difference Adverse events similar in both groups 2 patients with CNS effects in L group, photosensitivity 5% L

Table 22. Chronic Bacterial Prostatitis

Quinolone (n)	Design	Important Criteria	Results
Lomefloxacin(L) 400mg qd (90) Ciprofloxacin(C) 500mg bid (83) Naber et al (reference #31)	Multicenter Randomized	Bacterial culture positive Signs and symptoms of infection	Predominant organism *E. coli* Bacterial eradication rates (80% L; 85% C) were similar as were cure rates (98% L; 89% C) Similar rates of adverse reactions (19% L; 22% C)

Table 23. Community Acquired Pneumonia

Quinolone (n)	Design	Important Criteria	Results
Gatifloxacin (G) 400mg IV or Po QD Levofloxacin (L) 500 mg IV or PO QD Sullivan, et al (reference #32)	Double-blind Randomized Multicenter	Hospitalized patients Left to investigator's discretion if patient received IV only, PO only or IV and PO	Clinical cure rates were G 96%, L 94% Bacterial eradication rate was G 98%, L 93% 30 documented S pneumoniae cases adverse events similar G was as effective as L in the empiric treatment of CAP

Table 24. Skin and Skin Structure Infections

Quinolone (n)	Design	Important Criteria	Results
Levofloxacin(L) 500mg qd (129) Ciprofloxacin (C) 500mg bid (124) Nicodemo et al (reference #33)	Multicenter Double-blind Randomized Parallel	Uncomplicated skin/skin structure infection Excluded if known resistance to study drug	Predominant organisms were *S. aureus* and *S. pyogenes* Clinical cure/improvement similar 96.1(L) 93.5%(C) Bacterial eradication 93%(L) 89.7%(C) GI events occurred in both groups –12 L patients and 11 C patients.
Levofloxacin(L) 500mg qd (182) Ciprofloxacin (C) 500mg bid (193) Nichols et al (reference #34)	Randomized, non-blind Multicenter	Uncomplicated skin and skin structure	Predominant organisms were *S. aureus* and *S. pyogenes* Clinical success 97.8%(L) vs. 94.3% (C) Bacteriological eradication 97.5%(L) vs. 88.8%(C) Adverse events similar for both groups 6% vs 5% (L vs C)

Table 25. Acute Pyelonephritis

Quinolone (n)	Design	Important Criteria	Results
Levofloxacin(Le) 250mg qd (89) Ciprofloxacin(C) 500mg bid (58) Lomefloxacin(Lo) 400mg qd (39) Richard et al (reference #24)	Two studies pooled results for analysis Multicenter Randomized Double-blind,placebo-controlled(ciprofloxacin vs. levofloxacin) Open-label (lomefloxacin vs. levofloxacin)	Pyuria, $\geq 10^5$ cfu/ml Must be present Flank pain, costovertebral angle tenderness, fever may or may not be present	Predominant organism was *E. coli* Eradication rates similar 95%(Le) 94%(C) 95%(Lo) Relapse rates were similar Clinical cure (microbiologic and clinical success) rates 92%(Le) 88%(C) 80%(Lo) Rates of clinical success (cure plus improvement) were similar Adverse events 2%(Le) 8%(C)5%(Lo)

X. SUMMARY OF EFFICACY AND SAFETY[1-34]

Very few head to head comparative clinical studies exist with the fluoroquinolones. Therefore it is difficult to determine comparative efficacy for many indications. Because of the increasing antimicrobial spectrum of activity with the newer drugs in this class, it has been suggested that a classification similar to that of the cephalosporins be used to stratify the fluoroquinolones. Trials should be conducted within these groups to determine comparative clinical efficacy.

The fluoroquinolones are effective in treating both gram-positive and gram-negative infections. Currently, ciprofloxacin is FDA-approved for treating most types of infections. All of the fluoroquinolones are effective in treating urinary tract infections caused by susceptible organisms. Ciprofloxacin remains effective in treating both urinary tract and systemic infections caused by *P. aeruginosa*, however the use of this agent continues to be limited by the increasing rates of resistance.

Clinical failures have been reported with the use of ciprofloxacin and ofloxacin for the treatment of community acquired pneumonia caused by *S. pneumoniae*. The newest additions to this class exhibit more gram-positive activity and are effective in treating patients with community acquired pneumonia. The potential for the emergence of resistance to these agents still remains. This resistance could be increased by the use of more broad spectrum antibiotics to treat gram-negative infections. The newer fluoroquinolones also possess activity against the atypical pathogens associated with community acquired pneumonia. Additionally, the pharmacodynamic profile (AUIC's and Peak:MIC ratio) of the newer agents provide evidence for an advantage of these agents in treating *S. pneumoniae*.

Levofloxacin and ciprofloxacin have demonstrated similar efficacy in the treatment of skin and soft tissue infections. Ofloxacin has also been successful in treating these infections.

Anthrax comment in the IDSA guidelines for treating CAP:
"…empirical treatment before sensitivity tests of the responsible strain should be oral or IV ciprofloxacin, with doxycycline or penicillin as an alternative. Ciprofloxacin and doxycycline are advocated, because they are highly active *in vitro* and have established efficacy in the animal model. Other fluoroquinolones are probably equally effective. These factors are emphasized because of the possibility that regional supplies may be limited with large-scale exposures."

The most common complaints with the fluoroquinolones are gastrointestinal disturbances and central nervous system effects. Cartilage damage has been reported with the use of fluoroquinolones in immature animals. The safety and efficacy of the fluoroquinolones have not been established in patients under the age of 18 years old, pregnant women, and lactating women.

As with any antimicrobial agent, practitioners must individualize therapy based on the susceptibility patterns within their institution. Fluoroquinolones should be prescribed only when it is considered the drug of choice for a specific infection. Indiscriminant use of these drugs will result in the emergence of resistant organisms. Additionally, there are several less expensive alternative agents to the fluoroquinolones which should be employed whenever possible.

XI. CRITERIA FOR FORMULARY SELECTION

Clinical efficacy and bacterial eradication for a specific infection must be demonstrated in randomized, double-blind trials which compare these agents.

Acceptable safety profile, including drug interactions and disease state interactions.

Once-daily dosing regimen is preferred.

Availability of an intravenous and oral dosage form is preferred.

Administration without regard to meals is preferred.

Current antibiograms will be considered.

Availability of sensitivity testing using automated methods.

XII. RECOMMENDATIONS

The type and number of head to head trials among the fluoroquinolones does not enable a determination of the "best" agent. Overall, gatifloxacin and levofloxacin may offer advantages over the other agents. These agents display an expanded gram-positive spectrum of activity and improved pharmacokinetic and pharmacodynamic profiles. The in vitro advantage of gatifloxacin and moxifloxacin in treating *S. pneumoniae* has yet to be proven clinically. All of the fluoroquinolones have reports of resistant organisms. The safety concern with QT prolongation needs further investigation. Clinically significant QT prolongation has been associated with moxifloxacin. Though gatifloxacin has not displayed the finding, it carries the same package insert warnings as moxifloxacin. Since the number of patients treated with these newer agents is limited, the true occurrence of the effect may still need to be realized. On the other hand, levofloxacin has not been associated with QT prolongation in preclinical or clinical trials, does not carry the same package insert warning and has a larger patient exposure base to extarpolate from. In terms of other adverse effects, these are mild in severity, usually self limited and infrequently result in treatment discontinuation. Therefore, it appears that tolerability is not an issue of concern or difference between the fluoroquinolone agents.

The three agents which cover the greatest number of indications and display the least amount of adverse effects are ciprofloxacin, levofloxacin and gatifloxacin. Ciprofloxacin is not therapeutically interchangeable with gatifloxacin or levofloxacin. It must be dosed twice daily as opposed to once a day, it has poor coverage for *S. pneumoniae* and has several clinically significant drug interactions. Generic formulations of ciprofloxacin will soon be entering the market. Several have been FDA approved and AB rated to the innovator product. With these factors in mind it would be the most appropriate to identify either levofloxacin or gatifloxacin as a "workhorse" agent. These two agents would provide a broad spectrum of activity, good activity against *S pneumoniae* and low incidence of adverse effects. The newer agents should not be used as substitutes for ciprofloxacin in the cases of pseudomonas infections, febrile neutropenias or other serious gram negative infections.

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